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Dietary dilemmas over fats and cardiometabolic risk

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Dietary dilemmas over fats and cardiometabolic risk

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Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; COMA, committee on medical aspects of food and nutrition policy; DGAC, US Dietary Guidelines Advisory Committee; FAO, food and agriculture organisation; HbA1c, heamoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MUFA, monounsaturated fatty acids; NACNE, National Advisory Committee for Nutrition Education; NDNS, National Diet and Nutrition Survey; PUFA, polyunsaturated fatty acids; RNI, recommended nutrient intake; RR, relative risk; RCT, randomised control trial; RNI, Reference Nutrients Intakes; SACN, Scientific Advisory Committee on Nutrition; SFA, saturated fatty acids; TAG, triacylglycerol; TC, total cholesterol; WHO, world health organisation.

Abstract

Cardiovascular diseases (CVD) remain the greatest cause of death globally, and with the escalating prevalence of metabolic diseases, including type-2 diabetes, CVD mortality is predicted to rise. While the replacement of saturated fatty acids (SFA) has been the cornerstone of effective dietary recommendations to decrease CVD risk since the 1980s, the validity of these recommendations have been recently challenged. A review of the evidence for the impact of SFA reduction, revealed no effect on CVD mortality, but a significant reduction in risk of CVD events (7-17%). The greatest effect was found when SFA was substituted with polyunsaturated fatty acids (PUFA), resulting in 27% risk reduction in CVD events, with no effect of substitution with carbohydrate or protein. There was insufficient evidence from randomly controlled trials to conclude upon the impact of SFA replacement with MUFA on CVD and metabolic outcomes. However, there was high quality evidence that reducing SFA lowered serum total, and specifically low-density lipoprotein cholesterol, a key risk factor for CVD, with greatest benefits achieved by replacing SFA with unsaturated fats. The exchange of SFA with either PUFA or monounsaturated fatty acids, also produced favourable effects on markers of glycaemia, reducing HbA1c, a long-term marker of glycaemic control. In conclusion, the totality of evidence supports lowering SFA intake and replacement with unsaturated fats to reduce the risk of CVD events, and to a lesser extent, cardio-metabolic risk factors, which is consistent with current dietary guidelines.

Introduction

Cardiovascular diseases (CVD), which include coronary heart disease (CHD), cerebral vascular disease and peripheral vascular diseases, are the greatest cause of mortality in the world, with an estimated 158,000 deaths annually in the UK alone (1). In parallel, the epidemic of metabolic diseases, principally type 2 diabetes, and obesity contribute to an increase in risk from CVD. In England, 58% of women and 65% of men are overweight or obese, with the prevalence of obesity increasing from 15% to 26% between 1993 and 2016 (2). This rise in obesity directly contributes to the prevalence of type 2 diabetes. Of the estimated 6% of the UK population diagnosed with diabetes, 90% have type 2 diabetes, with a rapid increase in prevalence from 2.9% to 7.6%, and 1.9% to 6.2% among men and women respectively between 1994 and 2016 (3).

These chronic degenerative diseases are multifactorial, with a number of modifiable lifestyle risk factors. The Global Burden of Disease, Injuries, and Risk Factor study 2013 (4), includes data from 188 countries, and quantified modifiable risk factors to identify emerging threats to population health and opportunities for prevention. In the latest update, the quantified risks accounted for 88.7% disability-adjusted-life years (DALYs) lost from CVD and circulatory diseases and 76.4% from diabetes, the highest of all outcomes. Moreover, it was estimated that dietary risks were the greatest contributor to CVD and diabetes, accounting for 10.4 million deaths and 241.4 million DALYs (4). These, and other data, demonstrate the relevance of diet to CVD and metabolic risk and highlights the importance of dietary modulation to reduce this risk. This review will address the impact of dietary fats, particularly saturated fatty acids (SFA), on risk from these diseases.

Cardiovascular and cardio-metabolic risk factors

There is unequivocal evidence that reduction of total cholesterol (TC), and more specifically low density lipoprotein-cholesterol (LDL- C) significantly reduces the incidence of myocardial infarction and death from cardiovascular causes, without adversely affecting the risk of death from all causes in primary and secondary prevention studies (5). The European Atherosclerosis Society Consensus Panel reviewed the evidence for the effects of high LDL-C

on the development of CVD, including CHD and stroke and showed a clear linear causal relationship as illustrated in Figure 1 (5). A consensus was reached that serum LDL-C increased the progression of atherosclerosis in a dose-dependent manner, with greater detriment arising from longer exposure of the vascular endothelium to LDL-C (5). Evidence also clearly demonstrates that small dense LDL particles, which are more likely to move into the vascular intima, undergo oxidation and contribute to the atherosclerotic plaque are more atherogenic and confer a greater risk for CVD (6). In contrast, a low concentration of serum high density lipoprotein-cholesterol (HLD-C) is related to an increased risk of CHD (7), is a key feature of the metabolic syndrome and is highly prevalent in type 2 diabetes and obesity (8). HDL particles are involved in a process of 'reverse cholesterol transport', in which cholesterol is removed from tissues and organs and returned to the liver for metabolism (7). However, recent evidence has shown that increasing serum HDL-C, by use of drugs, may not result in the anticipated reduction in CVD risk, which is more closely related to the functionality, rather than the cholesterol content of HDL particles (9). However, the TC:HDL-C ratio is considered a more sensitive and specific CHD risk predictor than individual cholesterol measures; at all ages in women and the only lipid predictor independently related to CHD in men 65 to 80 years old (7, 10).

Hypertension is the greatest contributor to death globally and a key CVD and metabolic risk factor that is modifiable by diet (11). While the importance of lowering salt intake to reduce blood pressure is well founded (12), evidence for the impact of dietary fats on blood pressure and vascular function is lacking (13). The health of the vasculature and endothelial function is important for CVD risk reduction and inextricably linked to blood pressure. Endothelial dysfunction occurs when the balance between endothelial injury and repair is disrupted. Circulating bone marrow-derived endothelial progenitor cells play an important role in preserving the structural and functional integrity of the endothelium by inducing neovascularisation at the site of vascular injury (14). Reduced endothelial progenitor cell number and function have been associated with CVD risk factors, including hypertension and hypercholesterolemia, and their potential role as prognostic and/or diagnostic markers of CVD is of considerable value (14). Microparticles are small vesicles released from the surface of many cell types, including endothelial cells and platelets, during activation or apoptosis, which often occurs during endothelial injury. Microparticle numbers are elevated

in individuals with CVD and associated risk factors (15), and the addition of endothelial microparticle numbers to the Framingham risk score has been shown to improve its predictive power of future CVD events (16).

Central obesity and insulin resistance are defining characteristics of the metabolic syndrome, the other two of which can include raised plasma TAG, reduced HDL-C concentrations and hypertension (Table 1) (8). Those with the metabolic syndrome are estimated to have an increased risk of CVD and particularly type 2 diabetes with many shared metabolic risk factors, often presenting with relatively normal TC and LDL-C concentrations (8). There is evidence to suggest that diet and lifestyle interventions may be more effective in preventing the development of the metabolic syndrome than pharmacological agents, and dietary fats may play a key role in this respect (17). The evidence for the impact of dietary fat on cardiovascular and cardio-metabolic risk, with particular reference to SFA, will be reviewed and presented in an attempt to resolve the perceived inconsistencies and confusion.

SFA as a strategy to reduce CVD and cardio-metabolic risk factors

SFA reduction has been the mainstay of dietary fat recommendations for coronary heart disease (CHD) risk reduction for many decades. UK public health advise on SFA was officially introduced in 1983 in the National Advisory Committee for Nutrition Education (NACNE) report (18), which recommended reducing SFA to no more than 10% total energy. The Committee of Medical Aspects (COMA) re-evaluated the evidence in 1991 and 1994 and in these reports the advice to reduce SFA intake to no more than about 10% total energy was based on evidence that “increasing or decreasing the contribution of SFA to dietary energy is followed by a rise or fall in low density lipoprotein (LDL) cholesterol and in the commensurate risk of coronary heart disease” (19, 20). Since the 1990’s the evidence for the effects of SFA on a range of health outcomes has increased considerably. This has been reviewed by numerous international organisations with most proposing similar recommendations to limit SFA. Currently, the Australian Government Department of Health and New Zealand Ministry of Health (21) recommend SFA should contribute between 8-10% energy; the Food and Agriculture Organization/World Health Organization (FAO/WHO) (22),

Nordic Council of Ministers (23) and US Dietary Guidelines Advisory Committee (DGAC) (24) recommend no more than 10% energy as SFA and the European Food Safety Authority (EFSA) (25) recommend consuming as little as possible. All advise replacement of SFA with polyunsaturated fats (PUFA). In contrast, the French Food Safety Agency (AFSSA) (26) recommended a total SFA intake of no more than 12% energy, but specify a maximum intake of 8% energy from specific SFAs due to their atherogenic potential, namely lauric, myristic and palmitic acids. In 2015, a novel strategy for dietary advise was proposed by the Health Council of the Netherlands (HCN) (27) in which recommendations were designed around foods and dietary patterns rather than specific nutrients. In these recommendations, advice that related to SFA included: i) replace butter, hard margarines, and cooking fats by soft margarines, liquid cooking fats, and vegetable oils; ii) limit the consumption of red meat, particularly processed meat and iii) a few portions of dairy produce daily, including milk or yogurt. The evidence for SFA and health outcomes is currently under review by the Saturated Fats Working Group of the UK Scientific Advisory Committee on Nutrition (SACN). A draft report from SACN was released for public consultation in July 2018 with recommendations that the dietary reference value for SFA remain unchanged at population average of no more than 10% energy from SFA, with recommendations for SFA substitution with unsaturated fats (28).

Population intake data

Despite long standing dietary recommendations to limit SFA intake, very few populations comply with this advice. A study which included fatty acid intake data from 40 countries throughout the world reported that only 11 met the SFA (<10% energy) and 20 met the PUFA (6-11% E) recommendations. Furthermore, in 18 of 27 countries examined, more than 50% of the population had SFA intakes >10% E, whereas in 13 of 27 countries, the majority of the population had PUFA intakes <6% (29). The current SFA intake from the latest data from the UK NDNS (years 7-8) supports these data, with the mean consumption of SFA above recommendations in all age groups with SFA intakes of 11.9%, 12.5% and 14.3% of total dietary energy in adults aged 19-64, 65-74 and 75+ years, respectively. The mean population intakes of different fatty acid classes and the UK Reference Nutrients Intakes (RNI) are shown in Table 2 and Table 3 respectively. The main contributor to SFA intake in

adults of all ages were meat and meat products, milk and milk products, and cereals and cereal products (half from pizza, biscuits, buns, cakes, pastries, fruit pies and puddings) with each food group contributing between 20-27% of total SFA intake. Fat spreads contributed 9%, 13% and 16% total dietary energy in those of 19-64, 65-74 and 75+ years, respectively. Interestingly intakes of total SFA increased with household available income, although generally these differences were small.

Assessment of risk and quality of evidence

The quality of evidence is important to consider when assessing risk. A hierarchy of evidence as represented by a pyramid, is generally accepted, as shown in Figure 2. Data from ecological studies, although helpful for hypothesis generation, is of limited quality and represents associations which are often linked with considerable potential confounding. Data from cohort studies, particularly longitudinal prospective cohort studies, can offer valuable insight into associations between dietary factors and key outcome measures, such as CVD mortality, but do not prove cause or effect. Furthermore, these studies are often associated with confounding including: dietary change over the follow-up period; reformulation of foods throughout the follow-up period (such as removal of trans fatty acids from the food chain which has occurred over the past decade); lifestyle factors including weight change, smoking status, amount of activity which are not fully accounted for; influence of other datary components; no consideration of the replacing macronutrient or of the quality of macronutrient (i.e wholegrain vs refined carbohydrates or n-3 polyunsaturated fatty acids (PUFA) vs n-6 PUFA) and reverse causality.

In contrast, evidence from randomly controlled trials (RCT) are considered to be of higher quality, with data demonstrating the effect of controlled dietary intervention, such as substitution of SFA with PUFA, on hard clinical outcomes (e.g. CVD morality) or validated risk markers (e.g. LDL-C). However, all studies investigating dietary fats can be limited by the sample size; duration of follow-up/intervention; study design; confounding by the presence of dietary trans fatty acids in some intervention foods (known to have a significant detrimental effect on CVD) in studies published before 1990s; and residual confounding. Systematic reviews and meta-analyses of particularly RCT, can offer high quality data, which represents the totality of the evidence available. However, there are potential limitations in

meta-analyses, such as the quality of the individual studies, criteria for study inclusion, differences in study design, participant inclusion, type and methods of intervention, which can result in inability or inappropriate study comparison and inconsistent findings between meta-analyses addressing the same question. It is therefore apparent that the type of evidence is of paramount importance and wherever possible, rigorous, current and comprehensive systematic reviews and meta-analyse will be used in this review, although individual studies will also be included where appropriate.

Challenges to the SFA recommendations

As discussed above, there are consistent global dietary recommendations to limit SFA intake for disease risk reduction, which are based on rigorous assessment of the totality of evidence from RCTs and prospective cohort studies, yet within the last 5 years the validity of SFA reduction has been questioned. This recent challenge to the SFA recommendations has been in response to a number of systematic reviews and meta-analyses which indicate that there is limited evidence for the significant effects of SFA reduction on CVD mortality (30-34). These data will be discussed in the context of the quality and relevance of the evidence.

SFA and CVD risk

There is consistent evidence from systematic reviews and meta-analyses of RCTs (35, 36) and prospective cohort studies (30, 32, 33, 37, 38) for the lack of a significant relationship between SFA intake and CVD, CHD and stroke mortality, which has fuelled the recent challenges to SFA recommendations. However, a significant 17% reduction in CVD events in those who reduced their SFA intake compared with usual diet (using a random-effects statistical model) was reported in the most comprehensive, up-to-date and rigorous systematic review and meta-analysis of RCTs (35). This analyse included 11 studies with 53,300 participants and 4377 CVD events and used the gold-standard Cochrane protocol for systematic review. Furthermore, a significant 7% or 8% reduction was also observed after using two fixed-effect statistical models (Mantel-Haenszel and Peto, respectively), suggesting that reducing SFA intake to approximately 10% energy significantly reduces CVD events by between 7-17% (35).

Moreover, Hooper found a significant 7-8% reduction in CHD events when reduced intakes of SFA were compared with usual intakes after fixed effects analysis and a non-significant trend for a 13% reduction after random effects analysis (P=0.07) using 12 RCTs, that included 53,199 participants and 3307 cases. In contrast (30), Chowdhury and colleagues, in their high profile systematic review and meta-analysis of 20 prospective cohort studies (including 283,963 participants and 10,518 CHD cases), concluded there was no association between SFA intake and CHD outcomes, when the top verses the bottom tertiles of SFA intakes were compared using a random effects model. However, the authors also performed a fixed-effect statistical model and found a significant 4% increased risk of CHD outcomes when higher verses lower saturated fat intakes were compared, although this finding was not commented upon in their paper. The reporting of both random and fixed effects models is becoming increasingly popular as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (http://training.cochrane.org/handbook). However, within the scientific community there are inconsistencies in the application and relevance of these models to different datasets, with differences in the underlying assumptions and statistical considerations. Fixed-effect models give weight in direct proportion to the size of the primary studies, whereas random-effects models generally give similar weight to all studies, irrespective of size. Although random effects models are used more commonly, fixed-effect models may offer a number of advantages over random-effects models, such as proportionate study weighting, and it would seem prudent to consider both models when reviewing the evidence. The increase in CHD outcomes from higher SFA intake from prospective cohort studies (30) supports the analysis of RCTs using fixed effects analysis (35), and suggests reduction of dietary SFA would be of benefit.

Reducing SFA was found to have no effect on the mortality from stroke in a meta-analysis of RCTs (35) and also on ischaemic strokes from the most comprehensive systematic review with meta-analysis of 12 prospective cohort studies with 15 comparisons including n=339,090 participants and 6226 ischaemic stroke deaths (37). In contrast, a systematic review and meta-analysis of 15 prospective cohort studies (n=476,569 including 11,074 strokes) reported a significant 11% reduced overall stroke risk and 25% fatal stroke risk with higher SFA intake (39). Interestingly, after subgroup analysis there was no association in non-East Asian populations, but a significant association in East Asian populations (21%

lower risk) (39). In another meta-analysis of prospective cohort studies, a significant association was identified between lower SFA intake and higher intracerebral haemorrhagic strokes in Japanese populations only (40). These associations between higher SFA and reduced stroke seem to be isolated to East Asian populations living in East-Asia, who typically consume very low dietary SFA, have distinct differences in dietary patterns, other lifestyle factors and genetic background, in comparison to Western populations in Europe and America.

These studies provide vital evidence for the benefits of reducing intake of SFA on CVD and CHD risk, and to address the recent challenges to these recommendations. However, these studies are limited by the lack of consideration of which macronutrient replaced SFA in the diet, and could not distinguish between, or determine whether, there were any differential effects on CVD risk that were dependent on the substitute macronutrient. This is of paramount importance for the development of valid public health advice and guidance on practical strategies of SFA reduction and replacement.

Impact of the macronutrient replacement of SFA on CVD risk

Unlike pharmaceutical or supplemental studies, while a drug or supplement can be simply added to a participants' regimen and compared to a placebo, dietary interventions involving macronutrients require careful consideration in terms of the replacement macronutrient, particularly in an iso-energetic study design. This adds complexity to the implementation of the study, data analysis and interpretation of the results of a study. In reality, the intervention outcomes could be the result of reduction of one macronutrient, increase in the replacing macronutrient, or a combination of both.

SFA replacement with PUFA

The strongest evidence for the impact of SFA replacement with PUFA is from the comprehensive Cochrane systematic review with meta-analysis of RCTs performed by Hooper (35). This analysis revealed no effect of SFA reduction on CVD or CHD mortality, but a significant 27% lower risk of CVD events and 24% reduction in CHD events when SFA was replaced with PUFA, though no consideration was given to the type of replacement PUFA (35). An earlier meta-analysis also found a significant 21% reduction in risk of CVD mortality

when SFA were replaced with PUFA (n-6 and n-3 PUFA combined) and n-3 PUFA alone, but no effect on CVD mortality was observed when SFA was substituted with n-6 PUFA alone (34). Although a more recent systematic review with meta-analysis of 13 prospective cohort studies confirmed a significant 13% and 9% lower risk of CHD mortality and events, respectively, when 5% energy from SFA was replaced by the n-6 PUFA linoleic acid using fixed, but not random, effects models (41). Beneficial effects of SFA replacement with PUFA were also reported after a pooled analysis of 11 prospective cohort studies which showed that a 5% lower SFA and 5% higher PUFA was associated with a significant 26% lower CHD deaths and 13% lower CHD events (42). This was supported by another pooled analysis of 7 RCTs and one cross-over trial, in which the average weighted PUFA consumption was 14.9% energy and 5.0% energy in the intervention and control groups respectively. The overall pooled risk reduction was 19%, which was estimated to correspond to a significant 10% reduced risk of CHD events for every 5% of energy from SFA that was replaced with PUFA (43). After meta-regression analysis greater benefit was also shown from longer study duration (43).

Collectively these data provide consistent evidence that SFA replacement with PUFA reduces CVD and CHD events, and more limited evidence from prospective cohort studies only for a beneficial effect on CHD mortality. However, here was inadequate evidence on SFA replacement with PUFA on stroke.

SFA replacement with MUFA

Evidence for the impact of replacement of SFA for MUFA is extremely limited, with no systematic review or meta-analysis of RCTs. In the most relevant analysis of prospective cohort studies, a 5% lower energy intake from SFA and concomitant higher energy intake from MUFA was associated with a non-significant trend for higher CHD events, but not CHD deaths (42). The authors commented that there might have been significant confounding by trans fats from spreads, meat and dairy intake. Furthermore, no ‘P’ value was given and the confidence interval of 1.00 was stated, which suggests this did not reach statistical significance. These data are in stark contrast to the beneficial association reported from modelling of the dietary data from the Nurses Health Study and Health Professional Follow-up Study of 127,536 men and women with 24 to 30 years of follow-up and 7,667 incident

cases of CHD (44). This study showed that replacing 5% of energy from SFA with equivalent energy from PUFA or MUFA was associated with a significant 25% and 15% lower risk of CHD, respectively (44). Furthermore, a systematic review and meta-analysis of 32 cohort studies including 841,211 participants revealed a significant overall risk reduction of 12% for CVD mortality, 9% for CVD events and 17% for stroke when comparing the top versus bottom quartiles of MUFA, olive oil, oleic acid, and MUFA:SFA ratio combined. Interestingly, MUFA from mixed origin, animal and vegetable sources, was not associated with significant effects on outcome measures (45). These data support a beneficial impact of MUFA, but also highlight the limited RCT data and potential differential effects of MUFA from different foods, and the overall importance of investigating food sources in relation to CVD risk reduction.

SFA replacement with carbohydrate or protein

There is some evidence from the comprehensive Cochrane systematic review and meta-analysis of RCT, that replacement of SFA with total carbohydrate had no effect on CVD and CHD mortality and events, and limited evidence of no effect on strokes (35). A pooled modelling analysis of 11 prospective cohort studies (n=344,696) reported no association on CHD death, but significant 7% higher CHD events when comparing a 5% energy reduction in SFA and equivalent increase in carbohydrate (42). However, none of these analyses considered carbohydrate quality. In the modelling analysis of the Nurses Health Study and Health Professional Follow-up Study (n= 127,536) replacement of 5% energy from SFA with carbohydrates from whole grains was associated with a significant 9% lower risk of CHD, whereas replacing SFA with carbohydrates from refined starches/added sugars was not significantly associated with CHD risk(44). Further support of the importance of the quality of the carbohydrate and CHD risk was illustrated by analysis of n=53,644 participants of prospective cohort studies with a median of 12 year follow-up and 1943 incident MI cases (46). A non-significant inverse association between substitution of SFA with low GI carbohydrates was reported, yet a significant 33% higher MI risk from substitution with high GI carbohydrates was shown. This again highlights that macronutrient type and quality is of

key importance, and that SFA substitution with wholegrain intake are associated with beneficial effects on CHD risk.

There was limited evidence for a lack of effect of SFA substitution with protein on CVD and CHD mortality and events and stokes in the Cochrane systematic review and meta-analysis of RCTs in which most of the studies were not directly investigating SFA replacement with protein (35).

SFA and Cardio-metabolic risk

Type-2 diabetes

Evidence from systematic reviews and meta-analyses of prospective cohort studies indicate consistent evidence of no association between SFA reduction and risk of type-2 diabetes with the most comprehensive analysis including data from 8 studies (n= 237,454 participants and 8739 cases) when the highest vs lowest SFA intakes were compared (37). Only two prospective cohort studies addressed the association between SFA replacement with PUFA on type-2 diabetes, showing inconsistent results (38). One study reported a significant association of 16% reduction in type-2 diabetes risk, whereas the other found no association, unless the model was unadjusted for BMI, when a significant 12% reduction was observed, indicating the significant impact of adiposity on type-2 diabetes risk (38). No evidence was available for SFA replacement with MUFA and protein.

SFA and BMI

Reducing the intake of SFA was found to significantly reduce body weight and BMI in a systematic review with meta-analysis in adults (35). However, the majority of the data included in the analysis came from trials in which there were reductions in the intakes of both saturated and total fats, limiting specific attribution to SFA reduction. Furthermore, these anthropometric measures were not primary outcomes throwing considerable uncertainty of the results.

Fats, cardiovascular and cardio-metabolic risk markers

Dietary lipids

Dietary fats are key modulators of circulating lipids, with the reduction of serum LDL-C through SFA reduction and higher PUFA, particularly n-6 PUFA (linoleic acid) and shorter chain n-3 PUFA (alpha linoleic acid), and the serum triacylglycerol (TAG) – lowering effects of long chain n-3 PUFA from fish, fish oil or supplements, being central aspects of these dietary fat recommendations (Table 3).

The most comprehensive analysis investigating the impact of dietary fats, predominantly SFA and replacement macronutrient on serum lipoprotein concentrations was conducted by Mensink for the World Health Organisation (WHO) and published in 2016 (47). Mensink initially performed a systematic review, which identified 84 relevant studies, 211 diet data points and 2353 participants (65% men and 34% women) who had a mean age of 38 years (21 and 72 years), BMI 24.2 kg/m2 (20.0 to 28.6 kg/m2), TC 5.1 mmol/L (3.7 to 6.7 mmol/L); LDL-C of 3.3 mmol/L) (2.3 to 4.8 mmol/L); HDL-C of 1.2 mmol/L (0.9 to 1.8 mmol/L) and TAG of 1.2 mmol/L (0.7 to 2.2 mmol/L). After performing a number of multiple regression analyses it was shown that reducing SFA and replacing with a mixture of cis-PUFA (predominantly linoleic acid and α-linolenic acid) or cis-MUFA (predominantly oleic acid) was more effective than replacing SFA with a mixture of carbohydrates on the lipoprotein profile (Table 4). More specifically it was estimated that serum TAG increased by a mean 0.0011 mmol/L for every 1% energy SFA replacement with mixed carbohydrates, compared to a significant decrease in serum TAG of 0.004 mmol/L and 0.010 mmol/L for 1% energy replacement by *cis*-MUFA and *cis*-PUFA respectively. Furthermore, replacement of 1% energy from SFA with carbohydrate had no effect on serum TC:HDL-C ratio compared to a significant reduction of 0.027 and 0.034 after substitution with *cis*-MUFA and *cis*-PUFA respectively (Table 4). The results were consistent across a wide range of SFA intakes including less than 10% of total energy, consistent for both men and women and not effected by baseline lipid concentrations or type of intervention. Further analysis showed that there were differential lipid responses according to the type of SFA. In comparison to a mixture of carbohydrates, an increased intake of lauric, myristic or palmitic acid raised serum TC, LDL-C and HDL-C and lowered TAG concentrations, while an increased intake of stearic acid had no significant effect on these or other serum lipid values. Lauric acid alone reduced the TC:HDL-C and LDL-C:HDL-C ratios compared with a mixture of carbohydrates

(47). These data are supported by metabolic ward studies, which provide high quality data from carefully controlled study which involve provision of total dietary intake, with specific exchange of SFA for other macronutrients (48).

Vascular function and blood pressure

Hooper and colleagues offers the most comprehensive analysis on SFA and its replacement with other macronutrients on blood pressure and reported no significant effects (35). However, the evidence from this and a further systematic review without meta-analysis (49), is deemed limited, since blood pressure was a secondary outcome and not included in the search terms of the systematic reviews. More recently a RCT addressed the impact of 8% energy replacement of SFA with n-6 *cis*-PUFA or cis-MUFA for an 18-week intervention period in 195 men and women with 1.5-fold elevated CVD risk compared with the general population, with vascular function measures as the primary outcomes. It was reported that a high SFA diet (17% energy) increased night SBP (+3.8 ± 1.5 mmHg), while replacing 8% energy from SFA with n-6 PUFA and MUFA attenuated the elevated night SBP, which reached significance for replacement with *cis* MUFA (-1.1 ± 1.3 mmHg) (50). Furthermore, relative to the SFA-rich diet, replacing with *cis*-MUFA and *cis*-n-6 PUFA significantly decreased endothelial (-47.3%, -44.9% respectively) and platelet (-36.8%, -39.1% respectively) micro-particle numbers and increased endothelial progenitor cell numbers (+28.4%) when SFA was replaced with *cis*-MUFA (51). These data suggest that replacement of SFA with MUFA may beneficially affect endothelial repair and maintenance leading to reduced CVD risk. Moreover, an acute intervention in 32 post-menopausal women showed that postprandial DBP (incremental area under the curve-iAUC) was significantly lower when meal SFA was replaced with MUFA, with a similar trend for SBP reduction, and a corresponding lower plasma nitrite response (iAUC) (52). This evidence suggests a potential beneficial effect of replacing SFA with unsaturated fats, particularly cis-MUFA, although further robust RCT with vascular measures as primary outcomes are required to confirm these findings.

Glycaemic control

The most comprehensive evidence for SFA and glycaemic measures is by Imamura and colleagues in which a number of meta-regression analyses of various glycaemic and insulin resistant measures are presented (53). Data from 99 RCTs with 4144 participants, including individuals with and without type-2 diabetes were analysed and a significant lower fasting glucose (-0.04 mmol/L) was reported when 5% energy as SFA was iso-energetically substituted with PUFA, though no effect was shown with MUFA or carbohydrate substitution. A further meta-regression analysis of data from 23 RCTs with 618 participants reported that substitution of SFA with PUFA and MUFA significantly lowered serum HbA1c (a longer-term marker of glycaemic control) by a mean difference of -0.15% and -0.12%, respectively, with no effect of replacement with carbohydrate (53).

Data from 3 RCTs with 249 participants (with and without type 2 diabetes), reported a significant increase in the rate of clearance of blood glucose in a 2-hour oral glucose tolerance tests (OGTT) (a recognised measure of glucose tolerance) reporting a mean difference of -1.69 mmol/L (35). However, this was a secondary analysis and measures of glycaemic control were not included in the search terms. A more comprehensive systematic review with meta-regression analysis included data from 11 RCT with 615 participants, and showed that substitution of SFA with either PUFA, MUFA or carbohydrate had no effect on a 2-hour OGTT, or infusion measures (including hyperglycaemic or euglycaemic clamp and FSIGTT) (53). This finding is consistent with data from two of the largest RCTs that measured insulin sensitivity with an intra-venous glucose tolerance test as the primary outcome to investigate the effects of SFA replacement, with MUFA or carbohydrates of different quality (54, 55). However, meta-regression analysis of data on HOMA, a fasted marker of insulin resistance, from 30 RCTs with 1801 participants showed significant lower insulin resistance when SFA was substituted with PUFA and MUFA (mean difference -4.1% and -3.1% respectively) but not with carbohydrate (53).

Conclusions

There is consistent evidence that mortality from total CVD, CHD and stroke are not affected by SFA intake, and importantly no detriment to mortality from other causes from lower intakes (with the possible exception of strokes, particularly haemorrhagic strokes, in

population living in East Asia). However, there is good evidence for a reduction in CVD events with lower SFA intakes from RCTs and some evidence for risk reduction of CHD events for lower SFA intake from RCT and prospective cohort studies. Replacement with unsaturated fats, rather than carbohydrates or protein, has greater benefit to both CVD and metabolic risk, with more evidence for PUFA replacement. CVD and CHD events have a serious adverse impact on health and quality of life, and while mortality from CVD has decreased over the past 50 years in many Western populations, the prevalence of CVDs is increasing. With the escalating aging population, more people are living with cardiovascular and metabolic diseases, resulting in a major adverse impact on health, quality of life and a significant increase in financial burden to the NHS. Reduction in events would therefore have a significant benefit to society and beyond. This evidence supports our current recommendation to reduce SFA to promote public health. However, refinement of this guidance will require a greater understanding of how the sustainable replacement of SFA with different types of carbohydrates and unsaturated fats impacts on hard clinical endpoints, with address of the influence of sex and age.

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Authorship

JAL is the sole author of this manuscript.

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Adiposity	Must have central obesity Waist > 94 cm males > 80 cm females Plus 2 of the following:
Glycaemia	Fasting plasma glucose > 5.6 mmol/L
Dyslipidaemia	TAG >1.7 mmol/L Low HDL-C <1.03 mmol/L males < 1.29 mmol/L females or specific treatment
Hypertension	Systolic blood pressure > 130 mmHg Diastolic blood pressure > 85 mmHg

	or treatment

Table 2. Mean daily intake of saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids (%total energy) intake for UK children and adults by age. (NDNS RP survey years 7-8 (2014/15-2015/16) Bases unweighted.

Age Group	**SFA (%total eng)**	**MUFA (%total eng)**	**n-6 PUFA (%total eng)**	**n-3 PUFA (%total eng)**
Children 4-10 y n=514	10.0 ± 2.7	11.8 ± 2.1	4.3 ± 1.1	0.8 ± 0.3
Children 11-18 y n=542	12.4 ± 2.9	12.4 ± 2.4	4.7 ± 1.4	0.9 ± 0.3
Adults 19-64 y n=1082	11.9 ± 3.4	12.1 ± 3.0	4.7 ± 1.6	0.9 ± 0.4
Adults 65-74 y n=181	12.5 ± 3.6	11.3 ± 2.6	4.3 ± 1.4	1.0 ± 0.4
Adults 75+ y n=174	14.3 ± 3.9	11.6 ± 2.4	4.2 ± 1.6	1.0 ± 0.4

SFA: saturated fatty acid; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; %total eng: % total energy

Table 3. UK Dietary Reference Nutrient Intakes (RNI) for fats for adults as a percentage of total energy intake.

	Individual Minimum	**Population Mean**	**Individual Maximum**
SFA		10%	
cis-PUFA	n-3 PUFA 0.2% n-6 PUFA 1.0% LC n-3 PUFA 0.45g	6%	10%
cis-MUFA		12%	
trans fatty acids		2%	
Total fatty acids		30%	
Total fat		33%	

SFA: saturated fatty acid; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acid; LC n-3 PUFA, long chain n-3 polyunsaturated fatty acids. Taken from [19]

Table 4. Estimated multiple regression equations for the mean changes in serum lipids when 1% of dietary energy from SFA is isoenergetically replaced by carbohydrates, *cis*-MUFA or *cis*-PUFA

Lipid	**SFA for CHO**	**SFA for *cis*-MUFA**	**SFA for *cis*-PUFA**	**No[1]**
Change TC[2] (mmol/L) CI (95%)	**-0.041** -0.047 to -0.035 P <0.001	**-0.046** -0.051 to -0.040 P <0.001	**-0.064** -0.070 to -0.058 P <0.001	177/74
Change LDL-C (mmol/L) CI (95%)	**-0.033** -0.039 to -0.027 P <0.010	**-0.042** -0.047 to -0.037 P <0.001	**-0.055** -0.061 to -0.050 P <0.001	165/69
Change HDL-C (mmol/L) CI (95%)	**-0.010** -0.012 to -0.008 P <0.011	**-0.002** -0.004 to -0.000 P = 0.014	**-0.005** -0.006 to -0.003 P <0.001	163/68
Change in TAG (mmol/L) CI (95%)	**0.011** 0.007 to 0.014 P <0.001	**-0.004** -0.007 to -0.001 P = 0.022	**-0.010** -0.014 to -0.007 P <0.001	172/72
Change in TC:HDL-C ratio CI (95%)	0.001 -0.006 to 0.007 P = 0.842	**-0.027** -0.033 to -0.022 P <0.001	**-0.034** -0.040 to -0.028 P <0.001	159/66

SFA: saturated fatty acids; CHO: carbohydrates; *cis*-MUFA: *cis*-monounsaturated fatty acids; *cis*-PUFA: *cis*-polyunsaturated fatty acids; CI, confidence interval; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol;

[1]Number of diets/number of studies

[2] The 95% confidence intervals (CI) refer to the regression coefficients on the line directly above

Adapted from (47)

Figure 1 Log-linear association per unit change in low-density lipoprotein cholesterol (LDL-C) and the risk of cardiovascular disease as reported in meta-analyses of Mendelian randomization studies, prospective epidemiologic cohort studies, and randomised trials. The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and a cumulative effect on the risk of cardiovascular disease. Taken from (5)

Figure 2. Pyramid depicting hierarchy of evidence.